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How Dangerous Are Diuretics?

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Two major concerns that have been raised against the use of diuretics are: (a) diuretic-induced hypokalaemia may predispose to dangerous arrhythmias including sudden death (Kolata, 1982); and (b) long term diuretic use may cause an increase in serum cholesterol and thus an increased risk of arteriosclerosis, including coronary artery disease (Grimm et al., 1981).

Diuretics have provided the basic regimen for treating hypertension for many years and have served as the primary treatment in most of the controlled trials demonstrating the effectiveness of treatment. Although most physicians still believe that treatment for hypertension usually should begin with a thiazide diuretic, others are apt to try alternative regimens. This is due primarily to an increased concern with the potential risks of diuretic-induced hypokalaemia. These concerns resulted initially in a dramatic increase in the administration of potassium supplements or potassium-sparing diuretics, the cost of which in the USA totalled $250 million in 1981 alone (Harrington et al., 1982). Recently, because of fear of toxicity some physicians, especially in Scandinavia, have reduced the doses of hydrochlorothiazide to as low as 6.25 or 12.5 mg/day (e.g. Andrew et al., 1983; Berglund and Anderson, 1976).

Diuretics are the only known antihypertensive agents which lower blood pressure by reducing salt, water and extracellular fluid volume (Freis, 1976). Recent controlled trials indicate that when given as the sole treatment thiazide diuretics control blood pressure in approximately half of the patients treated (Veterans Administration Cooperative Study Group, 1982a,b,c, 1983), and in 85% of those given a diuretic plus a step-two drug (Editorial, 1977; Freis, 1976). Because they are effective, and certainly the least expensive of the antihypertensive agents, the validity of the charges against them needs to be carefully examined.

1. Diuretics and Hypokalaemia

1.1 Relationship Between Dose, Volume Depletion and the Antihypertensive Effects of Diuretics

There is a close association between volume reduction and the antihypertensive response to the diuretics. It has been known for many years that diuretics cause a moderate reduction in extracellular fluid volume and plasma volume, approximating 10 to 15% (Dustan et al., 1959; Wilson and Freis, 1959). This effect, although moderate, appears to play a major role in the reduction of blood pressure (Dustan et al., 1959; Freis, 1976). Volume loss occurs during the first 3 or 4 days of continuous treatment with diuretics after which no further volume depletion occurs (Freis, 1976; Papademetriou et al., 1984a). The net reductions in fluid volume are reflected in loss of bodyweight which approximates 1 to 2kg (Papademetriou et al., 1984a; Wilson and Freis, 1959). With respect to hydrochlorothiazide, doses of 50 mg/day were required to produce weight loss in most patients whereas lower

doses of 25 or 12.5mg did not result in significant weight loss (McGregor et al., 1983). Thus, in many patients, doses smaller than 50 mg/day would not be sufficient to lower volume effectively and probably blood pressure as well.

The antihypertensive effectiveness of long term drug therapy is often difficult to assess. Because of spontaneous decreases in blood pressure such studies need to be carefully controlled. Following repeated visits to the clinic, blood pressure often reverts back to normal levels without any drug treatment (Carey et al., 1976; Management Committee Australian Therapeutic Trial in Mild Hypertension, 1982), and without proper controls it may be impossible to differentiate spontaneous and drug-induced reductions in blood pressure.

A few studies have suggested that when low doses of hydrochlorothiazide are given with a β-blocker the dose-response curve becomes flat after 6.25 or 12.5 mg/day of hydrochlorothiazide (Andrew et al., 1983; Berglund and Anderson, 1976). However, it is difficult to judge the effectiveness of one drug when it is combined with another, especially when there is no control evaluation of either drug used alone (Andrew et al., 1983).

On the other hand there is considerable evidence to indicate that the antihypertensive response to hydrochlorothiazide alone does not become flat at low levels but rather continues to increase to quite high doses of the diuretic. For example, in the Veterans Administration Cooperative Study, propranolol alone was compared with hydrochlorothiazide alone in patients with mild hypertension. Doses of hydrochlorothiazide were titrated as needed from 25mg twice daily to 50mg twice daily and finally to 100mg twice daily until the diastolic blood pressure was controlled to <90mm Hg (Veterans Administration Cooperative Study Group, 1982a,b). Of the patients controlled on hydrochlorothiazide alone, 50% attained the goal diastolic pressure with the 25mg twice daily dose. However, 30% required the 50mg twice daily dose and 20% needed 100mg of the diuretic twice daily before their diastolic blood pressure fell to <90mm Hg. These doses are far in excess of the 6.25 or 25mg recommended by others.

Studies other than the Veterans Administration trial have found that the dose-response curve of hydrochlorothiazide also does not remain flat after small doses, and that doses as high as 100 mg/day are required in many patients (Anderson et al., 1984; Henning et al., 1980). It would appear from these results that different patients vary in their responsiveness to the diuretics and that while small doses are satisfactory in some patients they are inadequate in others. As with most antihypertensive agents, the optimal dose of a diuretic is probably best found by individual titration.

1.2 Diuretic-Induced Hypokalaemia and Ventricular Arrhythmias

Reluctance to employ standard doses of diuretics in treating patients with uncomplicated essential hypertension derives primarily from the possibility that diuretic-induced hypokalaemia may predispose to the development of life-threatening or even fatal ventricular arrhythmias (Kolata, 1982; Multiple Risk Factor Intervention Group, 1982).

Contrary to popular opinion, diuretic-induced hypokalaemia is not associated with a major loss of total body potassium. The hypokalaemia is limited almost exclusively to the extracellular compartment. Review of various studies indicates that during continuous thiazide treatment, losses of body potassium approximate only a biologically unimportant 5 to 7% of the total body content (Kassirer and Harrington, 1977). These small losses are in contrast to changes in extracellular potassium. which is reduced by about 20%. Because potassium concentrations within the cells are much greater than in extracellular fluid, large changes in extracellular potassium may exert only a small influence on total body potassium. The large difference between extra- and intracellular potassium levels is maintained by sodium-potassium metabolic pump activity (Haddy and Pamnami, 1984).

Whether selective extracellular hypokalaemia without significant change in intracellular potassium, such as occurs with diuretic-induced hypokalaemia, predisposes to increased risk of ventricular arrhythmias is not known. Although adequate

studies in experimental animals have not been performed (Harrington et al., 1982), the electrophysiological changes associated with selective extracellular hypokalaemia point towards a decreased rather than increased incidence of cardiac arrhythmias. According to the Nernst equation (Dyckner and Wester, 1979; Papademetriou, 1983) an increase in the intracellular/extracellular ratio which occurs in diuretic-induced hypokalaemia causes hyperpolarisation of the cell membrane. This raises the depolarisation threshold of the myocardium resulting in decreased rather than increased susceptibility of the heart to the development of arrhythmias. Hyperpolarisation of the cell membrane, however, may also raise conduction velocity which under special circumstances such as ischaemia, heart blocks or myocardial scars may either promote or retard re-entry phenomena. Regardless of these theoretical considerations, an increase in the ratio of intracellular/extracellular potassium of the type associated with thiazide diuretics has not been reported to produce life-threatening arrhythmias.

Diuretic-induced hypokalaemia may have differing physiological or pathological effects depending on the presence or absence of heart disease. For example, in the presence of congestive heart failure there may be a reduction in the intracellular concentration of potassium (Editorial, 1977). Localised changes in potassium may occur such as in acute myocardial infarction where high concentrations of potassium have been measured in the ischaemic zone (Hydegger et al., 1984). The elevated concentrations of potassium are thought to be the result of leakage of potassium from the injured cells. The role of whether diuretic-induced hypokalaemia in these special situations has not yet been clarified. This article, however, is not concerned with these forms of heart disease, but rather with the great majority of hypertensive patients who do not have overt heart disease and whose intracellular potassium content is apparently normal.

1.3 Hypokalaemia and Frequency of Ventricular Arrhythmias

The most practical and direct way of determining whether diuretic-induced hypokalaemia produces disturbances in cardiac rhythm is to carry out electrocardiographic monitoring. Using 48-hour continuous ambulatory monitoring, no association between hypokalaemia and the incidence of ventricular arrhythmias was found by Papademetriou et al. (1984b). Continuous electrocardiographic monitoring was carried out in patients with mild hypertension prior to any therapy and following hydrochlorothiazide treatment for 4 weeks. Patients were separated into those who developed hypokalaemia with thiazide therapy and those in whom serum potassium concentrations remained within the normal range. Following thiazide therapy no change was noted in either the frequency or severity of the arrhythmias in the patients who became hypokalaemic or those who remained normokalaemic. Other investigators using continuous electrocardiographic monitoring have confirmed the above findings (Leif et al., 1984; Madias et al., 1984). Further, in patients with overt hypokalaemia on long term diuretic therapy, administration of potassium supplements and potassium-sparing diuretics in amounts sufficient to raise serum potassium levels to normal had no effect on ventricular arrhythmias (Papademetriou et al., 1983).

A previous study by Holland et al. (1981) using electrocardiographic monitoring indicated that hypokalaemia secondary to the thiazides did increase the frequency and severity of ventricular arrhythmias. The difference between Holland's results and the more recent studies probably can be explained by differences in methodology. Holland excluded all patients who exhibited 6 or more ventricular premature beats/hour during the control period prior to thiazide administration. However, because of the great day-to-day spontaneous fluctuation in ectopic activity (Michelson and Morgenroth, 1980) the chances of these selected patients showing greater ectopic activity on the second (hypokalaemic) monitoring would be greatly enhanced simply by chance alone. Other investigators who did not select their patients on this basis found no increase in arrhythmias associated with the development of hypokalaemia (Leif et al., 1984; Madias et al., 1984; Papademetriou et al., 1984b).

Another previous study found an association between hypokalaemia and exercise-induced premature ventricular beats (Hollifield and Staton, 1981). The results are difficult to interpret, however, for a number of reasons: (a) the correlations were based on only 2- to 5-minute monitoring of arrhythmias which may be insufficient to distinguish chance occurrence of ectopic beats from those due to hypokalaemia; (b) the clinical significance of exercise-induced premature beats and their prognostic value is essentially unknown; and (c) the reproducibility of this method of assessing arrhythmias is very poor. This work has not been repeated and remains unconfirmed.

Additional concern with respect to diuretic-induced hypokalaemia has been generated by the recent observation that catecholamines which increase entry of potassium into cells may further aggravate the hypokalaemia resulting from treatment with thiazides (Struthers et al., 1983). However, these studies have not demonstrated that the hypokalaemia resulting from the combined effects of the diuretic and catecholamines has any effect on ventricular ectopic activity or that it increases either the frequency or severity of ventricular arrhythmias. As a result of catecholamine excess, potassium moves mostly into skeletal muscle cells with only minimal changes in potassium content of myocardial cells. The catecholamine-induced changes increase the ratio of intra- to extracellular potassium and theoretically at least should make the ventricle less rather than more susceptible to development of arrhythmias. Although catecholamines are known to increase ventricular arrhythmias they probably do so by other mechanisms than reduction in extracellular potassium.

1.4 Evidence from Clinical Trials

Most of the concern regarding the possible relationship between thiazide-induced hypokalaemia and sudden death has been generated by the results of the Multiple Risk Factor Intervention Trial (MRFIT) [Kolata, 1982; Multiple Risk Factor Intervention Trial, 1982]. It was suggested that data from MRFIT implicated thiazide diuretics as the cause for an increase in cardiac deaths in a subgroup of patients with minor electrocardiographic abnormalities. However, there are several problems with the interpretation of these data. The study was not designed to determine the relationship of cardiac deaths with respect to treatment with thiazide diuretics. The relationship between thiazide diuretics and sudden death was found after a retrospective search for correlations between many variables. This kind of retrospective procedure often leads to positive correlations by chance alone. Therefore, evidence so derived must be confirmed by independent studies. The results of other studies, however, have not been confirmatory.

Available data from similar trials such as The Hypertension Detection and Follow-up Program (HDFP) failed to confirm the findings of MRFIT. Thus, in HDFP no subgroup correlations were found between thiazide treatment and cardiovascular deaths (The Hypertension Detection and Follow-up Program, 1984). The HDFP investigators concluded that their results offered no support for the hypothesis raised in MRFIT that diuretics increase the mortality rates of patients with resting ECG abnormalities. The recently published morbidity-mortality results of the Medical Research Council Working Party (MRC Trial, 1985) indicated no significant differences between the effects of bendrofluazide in the prevention of all-cause mortality compared with propranolol ($p = 0.24$ and 0.71, respectively; cigarette smokers and non-smokers combined). Furthermore, in none of the studies (including MRFIT) has there been any correlation between diuretic dosage, serum potassium levels and deaths due to heart disease (Medical Research Council Working Party on Mild to Moderate Hypertension, 1983; MRFIT Trial, 1985).

The Medical Research Council Working Party on Mild to Moderate Hypertension (1983) reported 2 substudies with electrocardiographic monitoring. In one study without pretreatment baseline monitoring an increased incidence of ventricular ectopy occurred in hypertensive patients during long term treatment with thiazides compared to a group receiving only placebos. In this subgroup, however, there was no correlation be-

tween arrhythmias and serum potassium level, although there was a weak correlation with serum uric acid concentration. A second trial, better controlled, failed to confirm the first in that there was no increase in arrhythmias during treatment with thiazide diuretics for a period of 8 to 10 weeks.

The available evidence, therefore, fails to support the view that in patients without heart disease diuretic-induced hypokalaemia causes increased ventricular arrhythmias. But, because of the undue concern that has been generated, potassium replacement therapy has become widespread (Harrington et al., 1982), which if overdone could become potentially dangerous (Lawson, 1974).

2. *Diuretics and Serum Cholesterol*

Serum cholesterol usually increases slightly when thiazide diuretics are administered (Grimm et al., 1981). Some investigators have expressed concern that the elevation, even though slight, would over a period of many years aggravate and accelerate the development of coronary heart disease (Grimm et al., 1981). This fear would have some justification if it could be shown that the elevation of serum cholesterol is indeed persistent. The available evidence, however, indicates that it is not.

Three studies have shown that expected initial increases in serum cholesterol levels were followed later by reduction to or below the pretreatment levels. One of these trials was carried out in a Veterans Administration cooperative study in which 343 patients with mild hypertension received hydrochlorothiazide and no other drugs or dietary treatment (Veterans Administration Cooperative Study, 1982b). Plasma cholesterol rose during the first 3 months of treatment but at 12 months the cholesterol level fell to below baseline. Similarly, Alcazar et al. (1982) also found that plasma cholesterol only rose initially, and after 3 months returned toward the pretreatment baseline, remaining there for the next several years of observation. Data taken from the HDFP also indicated that the short term rise in plasma cholesterol was followed by a long term return to baseline (Williams et al., 1983). These observations are further supported by other studies which made only long term observations on changes in plasma cholesterol. When serum cholesterol levels were measured 1 or 2 years after beginning treatment they were not elevated in 2 studies (Amery et al., 1982; Kannel et al., 1977), but were elevated in 1 (Goldman et al., 1980).

Thus, elevated serum cholesterol concentration is not a risk during long term treatment with diuretics because the almost unanimous experience has been that elevation is not persistent after 6 months or 1 year of treatment.

3. *Summary and Conclusions*

The proposal that thiazide diuretics may increase cardiovascular risk receives no support from recent data. Current evidence does not indicate that diuretic-induced hypokalaemia is associated with increased ventricular arrhythmias. This evidence includes continuous electrocardiographic monitoring – which is the most sensitive technique for quantitating cardiac arrhythmias. In contrast to earlier reports, more recent studies found no evidence for increased arrhythmias during the period of hypokalaemia, or for decreased arrhythmic activity after correction of hypokalaemia. Similarly, studies claiming increased sudden death in patients on diuretic treatment have not been substantiated by the results of other large-scale trials.

Elevation of serum cholesterol concentrations with thiazide appears to be a short term phenomenon since most studies indicate the elevation reverts to baseline during long term treatment.

Thiazide diuretics remain as one of our most effective antihypertensive agents. Fears of their increasing the incidence of ventricular arrhythmias due to hypokalaemia, or constituting a risk factor for atherosclerosis by elevating serum cholesterol concentrations, appear largely unsubstantiated.

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